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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,269	02/22/2006	Ryuichi Morishita	003734-0059-101	7392

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EXAMINER	
LONG, SCOTT	

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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,269	MORISHITA ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-50,55,58,69-71,76 and 78-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-50,55,58,69-71,76 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/6/2008 has been entered.

Claim Status

Claims 47-50, 55, 58, 69-71, 76 and 78-80 are pending. Claims 47-50, 55, 58, 69, 76, and 78 are amended. Claims 1-46, 51-54, 56-57, 59-68, 72-75, 77, and 81-85 are cancelled. Claims 47-50, 55, 58, 69-71, 76 and 78-80 are under current examination.

Priority

This application claims benefit as a 371 of PCT/JP04/09838 (filed 07/09/2004). The application also claims benefit from foreign application PCT/JP2003/08740 (filed 07/09/2003). The instant application has been granted the benefit date, 9 July 2003, from PCT/JP2003/08740.

RESPONSE TO ARGUMENTS

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-50, 55, 58, 69-71, 76 and 78-80 remain rejected under 35 USC 103(a) as unpatentable over Lee et al. (FASEB Journal, 2001; 15:p.A663, #523.9 [provided in IDS filed 1/9/2006]) in view of Morishita et al. (US-6,262,033, issued 17 July 2001) and further in view of Debs et al. (US-5,641,662, issued 24 June 1997) and further in view of Cutie et al. (US-6,464,959, issued 15 October 2002) for the reasons of record and the comments below.

Applicant's arguments (Remarks, pages 8-10) and Claim amendments, filed 6 November 2008, with respect to the rejection of claims 47-50, 55, 58, 69-71, 76 and 78-80 under 35 USC 103(a) as unpatentable over Lee et al. in view of Morishita et al. and further in view of Debs et al. and further in view of Cutie et al. have been fully considered but they are unpersuasive.

The applicant argues that Morishita does not teach NF-kB is associated diseases such as Asthma. Contrary to the applicant's assertion, Morishita suggests that NF-kB is associated with asthma. Morishita teaches "diseases in which the therapeutic/ prophylactic composition of the invention is indicated are NF-kB-associated diseases…among such diseases…[are] lung diseases" (col.1, lines 54-65). Morishita et al. also teach "a variety of diseases, including asthma...[in which] either an overexpression or underexpression of one or a few proteins is a major etiologic factor in many cases. Moreover, a variety of transcriptional regulator factors such as transcription activators and transcription inhibitors are involved in the expression of proteins. NF-kB [is] a substance known to be one of such transcription regulatory factors" (col.1, lines 16-23). Consequently, the examiner concludes a skilled artisan

would understand Morishita et al. suggests that NF-kB is a transcriptional regulatory factor affecting expression of proteins which cause asthma. Furthermore, Morishita et al. deduced that affecting the expression of NF-kB would be useful in treating lung diseases.

The applicant further argues that the claim amendments have differentiated the particularly claimed respiratory diseases, "asthma, rhinitis, and COPD" from the lung diseases suggested for treatment by the cited art. The examiner finds this argument unpersuasive because the cited art suggest treating asthma by inhibiting NF-kB. Lee et al. teach "[t]he transcription factor nuclear factor (NF)-kappa B plays an important role in regulating many inflammatory diseases including asthma....These observation suggest that NF-kappa B activity plays in important role in the pathogenesis of asthma. Therefore a development of strategy to inhibit airway NF-kappa B activity may be beneficial for treatment of respiratory allergic diseases" (abstract). Lee et al. clearly suggest a link between NF-kB and asthma and further suggest treating asthma by inhibiting NF-kB using antisense. Therefore, the examiner finds the applicant's arguments unpersuasive.

The applicant argues that the remaining references do not make up for the deficiencies that Morishita lacks. As described in the pending rejection and above, Lee et al. in view of Morishita et al. and further in view of Debs et al. and further in view of Cutie et al. teach all the known elements of the instant claims and it would be obvious to combine them in known ways with no change in their respective functions. Therefore, the examiner finds the applicant's arguments unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 47-50, 55, 58, 69-71, 76 and 78-80 under 35 USC 103(a) as unpatentable over Lee et al. in view of Morishita et al. and further in view of Debs et al. and further in view of Cutie et al.

The examiner reiterates the pending rejection below:

Claims 47-50, 55, 58, 69-71, 76 and 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (FASEB Journal, 2001; 15:p.A663, #523.9 [provided in IDS filed 1/9/2006]) in view of Morishita et al. (US-6,262,033, issued 17 July 2001) and further in view of Debs et al. (US-5,641,662, issued 24 June 1997) and further in view of Cutie et al. (US-6,464,959, issued 15 October 2002).

Claim 47 is directed to a method for treating and/or preventing a disease, disorder or condition of the respiratory system due to expression of a gene regulated by NF-kB, comprising the step of: a) administration of a composition in the form of a dry powder, the composition comprising a double stranded oligonucleotide in a naked form and at least one excipient, which excipient is acceptable as a pharmaceutical additive for the dry powder, the composition being administered directly to the respiratory system of a subject suffering from the disease, disorder or condition wherein said double-stranded oligonucleotide consists of an oligonucleotide having a sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:3 and a oligonucleotide complementary thereto and wherein said disease, disorder or condition of the respiratory system id COPD, asthma or rhinitis.

Lee et al. teach administration of NF-kB p65 antisense oligonucleotide to an asthmatic mouse model, wherein treatment with the antisense oligonucleotide "resulted

in significant inhibitions of airway eosinophilia…and improvement of airway hyperresponsiveness." Lee et al. further suggest, a "strategy to inhibit airway NF-kappa B activity may be beneficial to treatment of respiratory allergic diseases." The specification teaches that a NF-kB decoy may be any oligonucleotide (page 24). The teachings of Lee et al. further satisfy the limitations of claims 46-47 (condition is airway inflammatory diseases, asthma). Although Lee et al. introduced the NF-kB decoy by intravenous injection, its activity has seen in the lungs, so the examiner interprets this as satisfying the limitation directed to administration to the respiratory system of the subject. Lee et al. teach "[t]he transcription factor nuclear factor (NF)-kappa B plays an important role in regulating many inflammatory diseases including asthma….These observation suggest that NF-kappa B activity plays in important role in the pathogenesis of asthma. Therefore a development of strategy to inhibit airway NF-kappa B activity may be beneficial for treatment of respiratory allergic diseases" (abstract). Lee et al. clearly suggest a link between NF-kB and asthma and further suggest treating asthma by inhibiting NF-kB using antisense.

Lee et al. do not teach the specific decoy, SEQ ID NO:1. Lee et al. also do not teach direct administration of the NF-kB decoy to the lung or nasal mucosa using a nebulizer, spray, respirator, or nasal drop. Lee et al. teach intravenous administration of NF-kB p65 antisense oligonucleotide.

Morishita et al. teach, not only the single stranded sequence NF-kB decoy, CCTTGAAGGGATTTCCCTCC, which is 100% identical to SEQ ID NO:1 of the instant application, but also suggest that the oligonucleotides of Morishita can be "double-

stranded" (col.2, lines 30-32). Furthermore, Morishita et al. teach, "a method for treating NF-kB-associated diseases which comprises administering to an animal an effective amount of a polynucleotide NF-kB chromosomal binding decoy which antagonizes NF-kB mediated transcription of a gene located downstream of a NF-kB binding site where in said polynucleotide comprises..." CCTTGAAGGGATTTCCCTCC (col.7, lines 51-56). In addition, Morishita et al. indicate that asthma is one of the diseases that can be treated with the NF-kB decoy (col.1, line 16). Morishita et al. also teach a variety of pharmaceutical carriers and preparations, including liposomes, powders and liquid solutions (col.3, lines 1-6) and stabilizers such as sucrose, lactose or starch, [claim 58]. Morishita et al. teach that asthma is a disease which is associated with NF-kB expression (Morishita et al., col.1, Background Art). Furthermore, Morishita et al. teach ischemic lung disease is affected by activation of genes under the control of NF-kB transcription (Morishita et al., col.1, lines 54-67).

Morishita et al. do not teach direct administration to the lung or nasal mucosa using a nebulizer, spray, respirator, or nasal drop.

Debs et al. teach, aerosol delivery of nucleic acids to cells of the airway and alveoli of the lung (abstract). Debs et al. describe nebulizers useful for airway delivery typical in the treatment of the airway inflammatory disease, asthma. [claims 48-50 and 79]. Debs et al. also describe intranasal delivery (col.38, line 30). Debs et al. also describe delivery of 1mg/treatment to about 500 mg/treatment (col.21, line 55) [claim 76].

The Lee, Morishita and Debs references do not teach dry powder administration using metered dose inhaler (MDI) or dry powder inhaler (DPI) to treat asthma, COPD or rhinitis.

Cutie et al. teach, delivery of drugs (including nucleic acids) to the lung by way of inhalation for treating asthma and chronic obstructive pulmonary disease (col.1, lines 17-21) having aerosol particle sizes of less than 10 μm in diameter (col.1, lines 26-27) [claims 69-71] and can be administered using a metered dose inhaler (MDI) or dry powder inhaler (DPI) (col.1, lines 31-32) [claims 69-71]. Cutie et al. also teach a method of treatment by nasal inhalation (col.10, lines 23-27) [claims 78-79] for treatment of rhinitis (col.8, line 46) [claims 80].

It would have been predictably obvious to the person of ordinary skill in the art at the time the invention was made to administer a particular NF-kB double stranded oligonucleotides comprising CCTTGAAGGGATTTCCCTCC and its complement, in a method for treating and/or preventing a disease, disorder and/or condition of the respiratory system (particularly asthma) using a nebulizer.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (treating asthma with double stranded NF-kB-specific oligonucleotides, the particular NF-kB oligonucleotide (CCTTGAAGGGATTTCCCTCC),

and using a nebulizer to administer agents to the lung for asthma treatments) are taught by Lee or Morishita or Debs or Cutie. In addition, methods of delivering nucleic acids using dry powder inhalation having micron diameter-sized particles were known in the art, as is illustrated by Cutie et al. It would be therefore predictably obvious to use a combination of these known elements in a treatment of asthma, rhinitis, and COPD with the particular NF-kB decoy, CCTTGAAGGGATTTCCCTCC and its complement.

Therefore the method as taught by Lee et al. in view of Morishita et al. and further in view of Debs et al. and further in view of Cutie et al. would have been *prima facie* obvious over the method of the instant application.

NEW GROUNDS OF REJECTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 47-50 and 78-79 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 19 of U.S. Patent Application No. 11/442585. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications recite methods of treating asthma with double-stranded polynucleotides comprising SEQ ID NO:1 (CCTTGAAGGGATTTCCCTCC) and its complement. Claim 1 and 19 of 11/442585 recites administration by nasal inhalation or intubation, while claim 47 of the instant application recites administering the composition in a dry powder form. Instant claims 48-50 recite methods of administration to respiratory system (claim 48), into airway (claim 48), by inspiration (claim 49), using an inhaler (claim 50), by nasal drop (claim 50) and nasal administration (claims 78-79). While the claims are not identical they encompass delivery of identical therapeutic molecules to the same parts of the body by the same or similar means.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633